Correction for urine glucose excretion

**Matsuda Index**

**Use of a SGLT-2 inhibitor**

\[
\text{HOMA-IR} = \frac{R_d}{(R_{au} - u)} \cdot \text{HOMA-IR}_u \\
\text{Matsuda index} = \sqrt{\frac{(R_{au} - u) \cdot (D - u_D)}{R_d} \cdot \text{Matsuda index}_u}
\]

where,
- HOMA-IR: true HOMA-IR, HOMA-IR$_u$: apparent HOMA-IR with urine excretion
- Matsuda index: true Matsuda index, Matsuda index$_u$: apparent Matsuda index with urine excretion
- $R_d$: rate of appearance of glucose without urine excretion
- $R_{au}$: rate of appearance of glucose with urine excretion
- $u$: urine glucose excretion during basal state
- $D$: glucose load (=75g/analyzed time [min])
- $u_D$: urine glucose excretion during oral glucose load (excreted during analyzed time [g/min])

During basal steady state, $R_d$ (glucose disposal) = $R_d$ = $R_{au}$ - $u$
($R_{au}$ may be increased by the elevated level of glucagon
J Clin Invest. 2014 Feb 3;124(2):509-14.)

\[
\text{HOMA-IR} = \frac{R_d}{(R_{au} - u)} \cdot \text{HOMA-IR}_u = \text{HOMA-IR}}_u \\
\text{Matsuda index} = \sqrt{\frac{(R_{au} - u) \cdot (D - u_D)}{R_d} \cdot \text{Matsuda index}_u} = \sqrt{\frac{(75 - u_D)}{75} \cdot \text{Matsuda index}_u}
\]

where,
- HOMA-IR: true HOMA-IR, HOMA-IR$_u$: apparent HOMA-IR with urine excretion
- Matsuda index: true Matsuda index, Matsuda index$_u$: apparent Matsuda index with urine excretion
- $R_d$: rate of appearance of glucose without urine excretion
- $R_{au}$: rate of appearance of glucose with urine excretion
- $u$: urine glucose excretion during basal state
- $D$: glucose load (=75g/analyzed time [min])
- $u_D$: urine glucose excretion during oral glucose load (excreted during analyzed time [g/min])
Correction for glucose dosage

Matsuda Index

\[
\text{Matsuda index} = \sqrt{\frac{D}{D_x}} \cdot \text{Matsuda index}_x
\]

\[
= \sqrt{\frac{D}{75}} \cdot \text{Matsuda index}_x
\]

where,
- Matsuda index: true Matsuda index
- Matsuda index$_x$: apparent Matsuda index with urine excretion
- D$_x$: actual glucose dose applied
- D: glucose load for Matsuda index (=75g)

Start from HOMA
Induction of HOMA-IR (1)

\[
\begin{align*}
\frac{dg}{dt} &= -k \cdot g + \frac{R_a}{V} \\
\frac{dk}{dt} &= -a_1 \cdot k + a_2 \cdot i
\end{align*}
\]

\( a_1, a_2 \) positive constant
\( g, i \) plasma glucose, insulin conc.
\( k \) the fractional disappearance rate of glucose (insulin action)
\( V \) the volume of distribution of glucose
\( R_a \) the glucose input rate

\( S_I = \frac{a_2}{a_1} \)

Induction of HOMA-IR (2)

\[
\begin{align*}
\frac{dg}{dt} &= -k \cdot g + \frac{R_a}{V} \\
\frac{dk}{dt} &= -a_1 \cdot k + a_2 \cdot i
\end{align*}
\]

Steady state:

\[
\begin{align*}
\frac{dg}{dt} &= 0 \\
\frac{dk}{dt} &= 0
\end{align*}
\]

Insulin sensitivity (steady state)

\[
S_I = \frac{k}{i} = \frac{a_2}{a_1} = \frac{R_a}{V \cdot g \cdot i} = \frac{R_a}{g \cdot i}
\]

\[
\text{HOMA-IR}_0 = \frac{1}{S_I} = \frac{g \cdot i}{\text{const}}
\]

(Radziuk J: J Clin Endocrinol Metab 85: 4426-4433, 2000)
**Induction of HOMA-IR_u with SGLT2I (1)**

\[
\begin{aligned}
    \frac{dg}{dt} &= -k \cdot g + \frac{R_a - u}{V} \\
    \frac{dk}{dt} &= -a_1 \cdot k + a_2 \cdot i
\end{aligned}
\]

In insulin sensitivity

\[ S_I = \frac{a_2}{a_1} \]

\( a_1, a_2 \) positive constant

\( g, i \) plasma glucose, insulin conc.

\( k \) the fractional disappearance rate of glucose (insulin action)

\( V \) the volume of distribution of glucose

\( u \) the glucose excretion rate from urine

\( R_a \) the glucose input rate


---

**Induction of HOMA-IR_u with SGLT2I (2)**

\[
\begin{aligned}
    \frac{dg}{dt} &= -k \cdot g + \frac{(R_a - u)}{V} \\
    \frac{dk}{dt} &= -a_1 \cdot k + a_2 \cdot i
\end{aligned}
\]

Steady state:

\[
\begin{aligned}
    \frac{dg}{dt} &= 0 \\
    \frac{dk}{dt} &= 0
\end{aligned}
\]

Insulin sensitivity (steady state)

\[ S_I = \frac{k}{i} = \frac{a_2}{a_1} = \frac{(R_a - u)}{V \cdot g \cdot i} = \frac{(R_a - u) \div V}{g \cdot i} \]

\[ \text{HOMA-IR} = \frac{1}{S_I} = \frac{g \cdot i}{\text{const'}} \]

\( g, i, \) and \( S_I \) are different from those when \( u=0 \).
If insulin sensitivity (steady state) is the same,

\[ \text{HOMA-IR}_u = \frac{g_{0u} \cdot i_{0u}}{\text{const}} \]

HOMA-IR, is calculated by using the same way as HOMA-IR.

If insulin sensitivity (steady state) is the same,

\[
\text{HOMA-IR} = \frac{1}{S_l} = \frac{1}{S_{l_u}} \\
= \frac{g_{0u} \cdot i_{0u} \cdot R_a \div V}{(R_{au} - u) \div V} \\
= \frac{R_a}{(R_{au} - u)} \cdot g_0 \cdot i_0 = (g_{0u} \cdot i_{0u}) \cdot \frac{R_a}{(R_{au} - u)}
\]

Oral glucose administration
After glucose administration

MCR (metabolic clearance rate)
\[
\frac{\text{Dose of glucose}}{\text{AUC of PG conc.}}
\]
(non-steady state)

After glucose administration

Insulin Sensitivity during OGTT

\[
\text{MCR of glucose} \div \text{Average Insulin conc.}
\]

\[
= \frac{\text{Dose of glucose}}{\text{PG} \times \text{Insulin}}
\]
Oral glucose administration
Basal with a SGLT-2 inhibitor

In response to glucose appearance (BASAL STATE)

\[ MCR + MCR_u = \frac{\text{Endogenous Glucose Production}[\text{mg/min}]}{\text{AUC of PG conc.}} \]

\[ MCR_u = \frac{\text{Urine Glucose Excretion [mg/min]}}{\text{AUC of PG conc.}} \]
**In response to glucose appearance**
*(BASAL STATE)*

Insulin Sensitivity during Basal State can be estimated by

\[
\frac{\text{MCR of glucose}_0}{\text{Average Insulin conc.}_0} = \frac{\text{EGP}_0}{\text{PG}_0 \times \text{Insulin}_0} = \frac{\text{EGP}_0}{k \times \text{HOMA-IR}}
\]

When UGE = 0,

\[
\text{HOMA-IR} = \frac{\text{PG}_0 \times \text{Insulin}_0}{k}
\]

\(k\): constant

---

**In response to glucose administration**
*(BASAL STATE)*

\[
\text{MCR}_u = \frac{\text{Endogenous Glucose Production}_u [\text{mg/min}]}{\text{AUC of PG conc.}_u} - \frac{\text{Urine Glucose Excretion} [\text{mg/min}]}{\text{AUC of PG conc.}_u}
\]

EGP: Endogenous Glucose Production
UGE: Urine Glucose Excretion
**In response to glucose appearance**

*(BASAL STATE)*

**Insulin Sensitivity during Basal State**

can be estimated by

\[
\frac{MCR_u}{\text{Average Insulin conc.}_u} = \frac{EGP_u - UGE}{PG_u \times \text{Insulin}_u} = \frac{EGP_u - UGE}{k \times HOMA-IR_u}
\]

\[HOMA-IR_u = \frac{PG_u \times \text{Insulin}_u}{k}\]

\[k: \text{constant}\]

If insulin sensitivity is the same despite of urine glucose excretion,

\[
\frac{MCR_u}{\text{Insulin}_u} = \frac{MCR_0}{\text{Insulin}_0}
\]

\[
\frac{EGP_u - UGE}{k \times HOMA-IR_u} = \frac{EGP_0}{k \times HOMA-IR_0}
\]

\[HOMA-IR_0 = \frac{EGP_0}{EGP_u - UGE} \cdot HOMA-IR_u\]
Oral glucose administration

Glucose loading with a SGLT-2 inhibitor

AUC of PG conc. (non-steady state) = Dose of glucose / AUC of PG conc. (non-steady state)

After glucose administration (OGTT)

MCR + MCRu

Glucose Dose
Endogenous glucose production = 0

MCR

Urine excretion (MCRu)

PG

mean

0 ~180min
After glucose administration (OGTT)

\[
MCR_u = \frac{\text{Dose of glucose \, [mg/min]}}{\text{AUC of PG conc.}_u - \frac{\text{Urine Glucose Excretion \, [mg/min]}}{\text{AUC of PG conc.}_u}}
\]

D: Dose of glucose
UGE: Urine Glucose Excretion

After glucose administration (OGTT)

Insulin Sensitivity can be estimated by

\[
\frac{MCR_u}{\text{Average Insulin conc.}_u} = \frac{D - UGE}{PG_u \times \text{Insulin}_u}
\]
If insulin sensitivity is the same despite of urine glucose excretion,

\[
\frac{\text{MCR}_u}{\text{Insulin}_u} = \frac{\text{MCR}_0}{\text{Insulin}_0}
\]

\[
\frac{D - \text{UGE}}{\text{PG}_u \times \text{Insulin}_u} = \frac{D}{\text{PG}_0 \times \text{Insulin}_0}
\]

Correction to Matsuda index

Glucose loading with a SGLT-2 inhibitor
When a SGLT-2 inhibitor is used,

\[
\text{Matsuda index}_h = \frac{10000}{\sqrt{g_{0u} \cdot i_{0u} \cdot g_u \cdot i_u}}
\]

\[
g_{0i_0} = (g_{0u} \cdot i_{0u}) \cdot \frac{R_a}{(R_{au} - u)} \quad g \cdot i = (g_u \cdot i_u) \cdot \frac{D}{(D-u_D)}
\]

\[
\text{Matsuda index} = \frac{10000}{\sqrt{g_0 \cdot i_0 \cdot g \cdot i}}
\]

\[
= \frac{10000}{\sqrt{(g_{0u} \cdot i_{0u}) \cdot \frac{R_a}{(R_{au} - u)} \cdot (g_u \cdot i_u) \cdot \frac{D}{(D-u_D)}}}
\]

When a SGLT-2 inhibitor is used,

\[
\text{Matsuda index}
= \frac{\text{Matsuda index}_h}{\sqrt{\frac{R_a}{(R_{au} - u)} \cdot \frac{D}{(D-u_D)}}}
= \sqrt{\frac{(R_{au} - u) \cdot (D-u_D)}{R_a \cdot \frac{D}{(D-u_D)}}} \cdot \text{Matsuda index}_h
\]